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Relationship Between Renal Function and Plasma Brain Natriuretic Peptide in Patients With Heart Failure

Takayoshi Tsutamoto, MD, Atsuyuki Wada, MD, Hiroshi Sakai, MD, Chitose Ishikawa, MD, Toshinari Tanaka, MD, Masaru Hayashi, MD, Masanori Fujii, MD, Takashi Yamamoto, MD, Tomohiro Dohke, MD, Masato Ohnishi, MD, Hiroyuki Takashima, MD, Masahiko Kinoshita, MD, Minoru Horie, MD

Otsu, Japan

OBJECTIVES This study sought to evaluate the relationship between brain natriuretic peptide (BNP), renal function, and the severity of congestive heart failure (CHF).

BACKGROUND Both BNP and renal function are prognostic predictors in CHF patients.

METHODS We measured the plasma BNP level in the aortic root and coronary sinus in 366 consecutive patients with CHF. Estimated glomerular filtration rate (eGFR) by the Cockcroft-Gault equation was used as an indicator of renal function.

RESULTS By stepwise multivariate analyses, hemodynamic parameters such as left ventricular ejection fraction (LVEF) and left ventricular end-diastolic pressure (LVEDP) but not eGFR were independent predictors of a transcardiac increase (coronary sinus-aortic root) in BNP. Regarding the plasma level of BNP in the aortic root, not only LVEF ($p < 0.0001$) and LVEDP ($p < 0.0001$) but also eGFR ($p < 0.0001$) were independent predictors. Patients were divided into two groups, patients with an eGFR ≥60 ml/min (group 1, n = 229) and patients with an eGFR <60 ml/min (group 2, n = 137). There was no difference in LVEF, LVEDP, or the transcardiac gradient of BNP between the two groups, but the plasma level of BNP in the aortic root was approximately two-fold greater in group 2 than in the group 1.

CONCLUSIONS These findings suggest that decreased clearance from the kidney contributes to the elevated BNP in CHF patients with renal dysfunction, especially in patients with an eGFR <60 ml/min. (J Am Coll Cardiol 2006;47:582–6) © 2006 by the American College of Cardiology Foundation

The plasma level of brain natriuretic peptide (BNP) is useful as an objective marker for the diagnosis of congestive heart failure (CHF) caused by systolic and diastolic dysfunction (1). A high plasma BNP level provides important prognostic predictors not only in patients with CHF (2) and acute coronary syndrome but also in the general population. Glomerular filtration rate (GFR) as well as BNP has been shown to be related to prognosis in patients with CHF (3). Therefore, the evaluation of BNP and estimated GFR (eGFR) is important to estimate the severity of CHF; however, the relationship between eGFR, BNP, and the severity of CHF has not been fully elucidated.

Plasma BNP is regulated by secretion from the heart and clearance from the circulation. The kidney is an important clearance organ for circulating BNP. To date, there has not been any report showing a direct relationship between renal function and cardiac BNP secretion in CHF patients. The present study evaluates whether renal function directly contributes to the elevated BNP in CHF patients and whether other factors such as age, gender, body mass index, anemia, and atrial fibrillation affect BNP secretion from the failing heart in CHF patients.

METHODS

Patients. The patients were 366 consecutive symptomatic CHF patients. Patients with acute myocardial infarction or those on dialysis therapy were excluded. Informed consent was obtained from all patients for participation in the study, after protocol approval by the Committee on Human Investigation at our institution.

Study protocol. Blood samples for measuring plasma BNP were collected simultaneously from the aortic root and coronary sinus. Renal function was represented by the eGFR according to the Cockroft-Gault equation. Plasma BNP concentrations were measured as previously reported (2).

Statistical analysis. All results are expressed as the mean values ± standard deviation. Chi-square test or analysis of variance was used to determine differences between groups. Univariate analyses were performed using the Student *t* test. Because BNP levels were not normally distributed, differences between the groups were detected by the Wilcoxon rank-sum test with two-tailed p values of <0.05, and log BNP was used in correlations and regression models. The difference of the intercept of the linear regression line between two groups was analyzed using analysis of covariance. A p value <0.05 was regarded as significant.

From Cardiovascular and Respiratory Medicine, Shiga University of Medical Science, Otsu, Japan. This study was supported by a Grant-in-Aid for Scientific Research in Japan.

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Abbreviations and Acronyms

BNP = brain natriuretic peptide
CHF = congestive heart failure
CKD = chronic kidney disease
eGFR = estimated glomerular filtration rate
GFR = glomerular filtration rate
LVEDP = left ventricular end-diastolic pressure
LVEF = left ventricular ejection fraction

RESULTS

Patient characteristics. Table 1 summarizes the patient characteristics according to eGFR.

Relationship between plasma BNP and renal function. There was a significant correlation between the eGFR and plasma BNP in the aortic root, but there was no significant correlation between the eGFR and the transcardiac increase in BNP (Fig. 1). In Table 2, only the left ventricular ejection fraction (LVEF) and left ventricular end-diastolic pressure (LVEDP) were independent predictors of cardiac BNP secretion. In Table 3, not only LVEF and LVEDP but also eGFR and hemoglobin were independent predictors of plasma BNP in the aortic root.

Correlation between hemodynamics and BNP: impact of renal function. There was no difference in LVEF, LVEDP, and the transcardiac gradient of BNP between the two groups, but the plasma level of BNP in the aortic root was approximately two-fold greater in the group 2 than in group 1 (Fig. 2). There were significant correlations between LVEDP, LVEF, and the transcardiac increase in BNP in both groups with the same regression line (Fig. 3A). The regression line between the LVEDP, LVEF, and log BNP in the aortic root of patients in group 2 showed a shift significantly upward compared with that of patients in group 1 ($p < 0.001$) (Fig. 3B). Figure 4 shows the effect of the interaction between New York Heart Association functional class and renal function on BNP level. The transcardiac increase in BNP was increased with the severity of CHF, but was not affected by the degree of renal function, whereas the plasma level of BNP was increased with the severity of CHF and was also independently affected by the degree of renal function ($p < 0.001$, on two-way analysis of variance).

Table 1. Patient Characteristics

	Total Group	90 ≤ eGFR	60 ≤ eGFR <90	40 ≤ eGFR <60	eGFR <40	p Value
Characteristics	(n = 366)	(n = 86)	(n = 143)	(n = 89)	(n = 48)	
Age, mean (SE), yrs	63.9 ± 12.3	51.7 ± 12.5	64.1 ± 9.6	71.7 ± 6.0	71.0 ± 10.9	<0.0001
Male, n (%)	269 (73)	72 (83)	108 (75)	58 (65)	31 (65)	<0.05
BMI (kg/m^2)	23.1 ± 3.7	25.3 ± 4.3	23.2 ± 3.0	21.8 ± 3.2	21.7 ± 3.2	<0.0001
NYHA functional class, n (%)						<0.05
I	45 (12)	6 (7)	21 (15)	12 (13)	4 (8)	
II	159 (43)	44 (51)	52 (36)	41 (46)	21 (44)	
III	112 (31)	18 (21)	51 (36)	27 (30)	9 (19)	
IV	50 (14)	18 (21)	19 (13)	9 (10)	14 (29)	
Etiology of heart failure						
Ischemic cardiomyopathy	227 (62)	46 (54)	89 (62)	65 (72)	27 (56)	<0.05
Dilated cardiomyopathy	72 (20)	25 (29)	28 (29)	14 (17)	5 (11)	<0.05
Hypertensive heart disease	67 (18)	15 (17)	26 (18)	10 (11)	16 (33)	<0.05
Hypertension, n (%)	188 (51)	38 (44)	77 (54)	43 (48)	30 (62)	0.188
Diabetes mellitus, n (%)	109 (30)	23 (27)	40 (28)	27 (30)	19 (40)	0.437
Heart rate, beats/min	70.1 ± 15.7	73.7 ± 17	68.4 ± 15.7	66.5 ± 12.4	75.6 ± 17.1	0.0004
Mean blood pressure, mm Hg	91.3 ± 16.5	92.2 ± 16.0	91.4 ± 16.2	90.6 ± 14.1	90.6 ± 22.1	0.917
LVEF, %	38.6 ± 11.2	36.2 ± 11.8	38.9 ± 11.6	40.1 ± 9.5	38.8 ± 11	0.127
LVEDP, mm Hg	12.2 ± 6.5	12.2 ± 6.1	12.1 ± 6.4	11.3 ± 5.9	14.1 ± 8.2	0.109
Creatinine, mg/dl	1.05 ± 0.84	0.72 ± 0.15	0.85 ± 0.17	0.97 ± 0.25	2.45 ± 1.7	<0.0001
eGFR, ml/min	72.1 ± 32.9	117.3 ± 26.7	73.7 ± 8.6	51.1 ± 5.5	26.0 ± 10.2	<0.0001
BNP in the AO, pg/ml	189.8 ± 305	125 ± 169	157 ± 185	165 ± 248	450 ± 608	
Median value	94	67.9	92.2	80	223.5	<0.0001
(CS-AO) BNP, pg/ml	228.9 ± 250	231 ± 274	219 ± 217	207 ± 224	295 ± 47	
Median value	150	155	156.8	132	200	0.342
Hemoglobin, g/dl	12.3 ± 1.9	13.6 ± 1.9	12.6 ± 1.5	11.6 ± 1.7	10.7 ± 1.9	<0.0001
Treatments						
Spironolactone, n (%)	87 (24)	19 (22)	30 (21)	21 (23)	17 (35)	0.252
Loop diuretics, n (%)	142 (39)	24 (28)	52 (36)	33 (36)	33 (69)	<0.0001
Digitalis, n (%)	78 (21)	21 (24)	30 (21)	12 (13)	15 (31)	0.082
ACEI or ARB, n (%)	245 (67)	58 (68)	102 (71)	60 (66)	25 (52)	0.121
Beta-blockers, n (%)	132 (36)	27 (31)	57 (40)	34 (37)	14 (29)	0.405

ACEI = angiotensin-converting enzyme inhibitor; AO = aortic root; ARB = angiotensin receptor blocker; BMI = body mass index; BNP = brain natriuretic peptide; CS = coronary sinus; eGFR = estimated glomerular filtration rate; LVEDP = left ventricular end-diastolic pressure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

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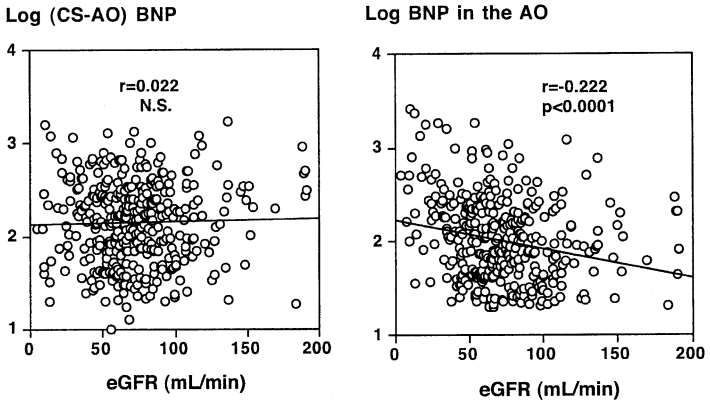

Figure 1. Relationship between the estimated glomerular filtration rate (eGFR) and the plasma log brain natriuretic peptide (BNP) secretion and the log BNP in the aortic root (AO). CS = coronary sinus.

Table 2. Univariate and Multivariate Linear Model of Transcardiac Increase in Log BNP

Variables	Univariate Correlation Coefficient	p Value	Multivariate Beta-Coefficient (SE)	p Value
Age	−0.166	0.0063		
Gender (male = 1)	−0.059	0.8137		
BMI	−0.130	0.1773		
Ischemic etiology (yes = 1)	−0.178	0.0121		
NYHA functional class	0.473	<0.0001		
Hemoglobin (g/dl)	−0.069	0.8728		
eGFR (ml/min)	−0.052	0.5928		
Rhythm (AF = 1, sinus = 0)	0.064	0.301		
Heart rate (beats/min)	0.209	0.0100		
Mean blood pressure (mm Hg)	−0.067	0.0001		
LVEDP (mm Hg)	0.510	<0.0001	0.040 (0.005)	<0.0001
LVEF (%)	−0.3564	<0.0001	−0.010 (0.03)	0.0001

Abbreviations as in Table 1.

Table 3. Univariate and Multivariate Linear Model of Plasma Log BNP

Variables	Univariate Correlation Coefficient	p Value	Multivariate Beta-Coefficient (SE)	p Value
Age	0.031	0.547		
Gender (male = 1)	−0.133	0.018		
BMI	−0.158	0.0024		
Ischemic etiology (yes = 1)	−0.222	<0.0001		
NYHA functional class	0.578	<0.0001		
Hemoglobin (g/dl)	−0.197	<0.0001	−0.029 (0.01)	0.0024
eGFR (ml/min)	−0.222	<0.0001	−0.003 (0.001)	<0.0001
Rhythm (AF = 1, sinus = 0)	0.187	0.0003		
Heart rate (beats/min)	0.195	0.0002		
Mean blood pressure (mm Hg)	−0.115	0.0275		
LVEDP (mm Hg)	0.665	<0.0001	0.040 (0.003)	<0.0001
LVEF (%)	−0.365	<0.0001	−0.007 (0.001)	<0.0001

Abbreviations as in Table 1.

DISCUSSION

The relationship among BNP, renal function, and the severity of CHF has remained unclear because there has not been a study examining cardiac BNP secretion in CHF patients with renal insufficiency. The present study has suggested the following: 1) If we evaluate the severity of CHF by plasma BNP, we should take into account renal clearance in patients with an eGFR <60ml/min. 2) Renal function had a more direct effect on circulating BNP than previously recognized, as shown in Figure 4. 3) Other factors such as age, gender, body mass index, and atrial fibrillation may not be the major factor of the plasma BNP if we concomitantly evaluate LVEF, LVEDP, hemoglobin, and renal function (eGFR) in CHF patients.

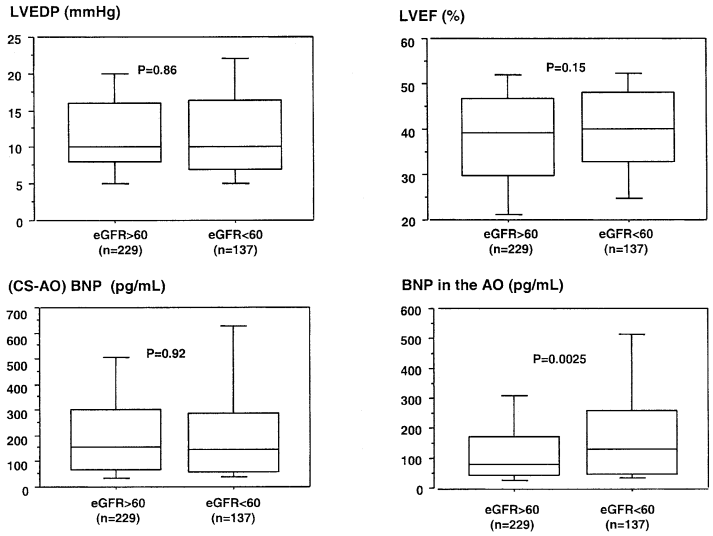

Figure 2. Comparisons between hemodynamic parameters and brain natriuretic peptide (BNP). The box defines the interquartile range with the median indicated by the crossbar. Group 1 = patients with an estimated glomerular filtration rate (eGFR) ≥60 ml/min; group 2 = patients with an eGFR <60 ml/min. AO = aortic root; CS = coronary sinus; LVEDP = left ventricular end-diastolic pressure; LVEF = left ventricular ejection fraction.

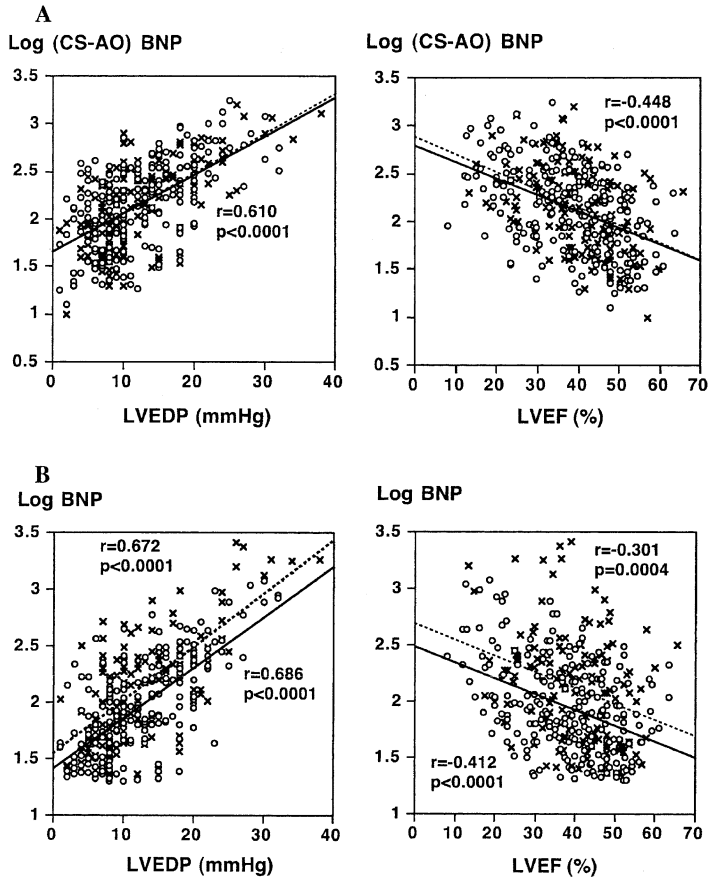

Figure 3. (A) Relationship between the log brain natriuretic peptide (BNP) secretion and hemodynamic parameters. **(B)** Relationship between log BNP in the aortic root (AO) and hemodynamic parameters. **Open circles** = group 1 patients; **cross marks** = group 2 patients; **solid lines** = patients in group 1; **dotted lines** = patients in group 2. There were significant correlations between left ventricular end-diastolic pressure (LVEDP), left ventricular ejection fraction (LVEF), and the transcardiac increase in BNP in both groups with the same regression line **(A)**. The regression line between the LVEDP, LVEF, and log BNP in the AO of group 2 showed a significant shift upward compared with that of group 1 **(B)**. CS = coronary sinus.

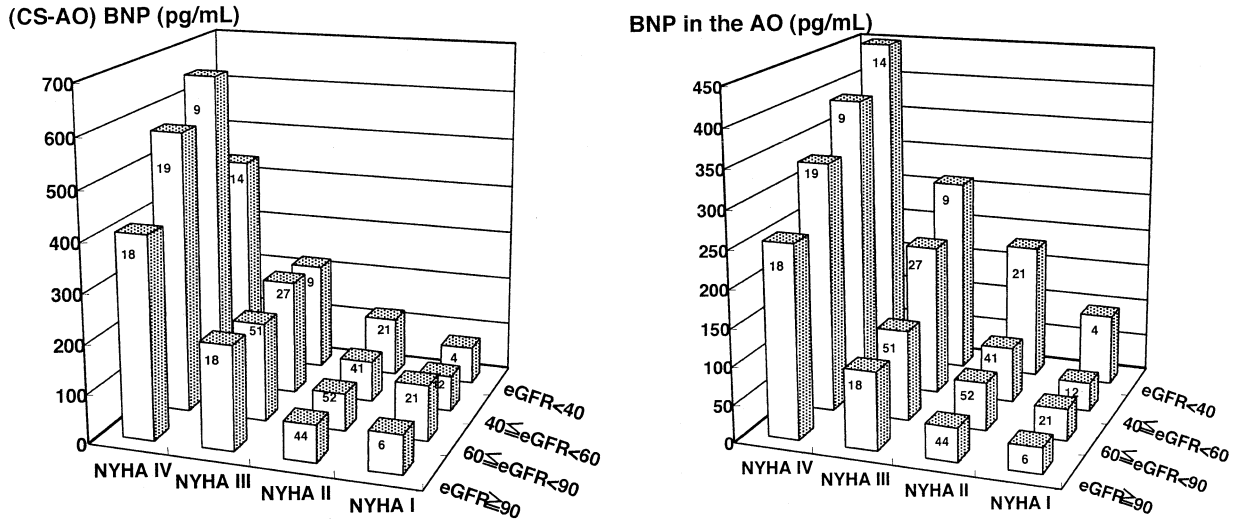

Figure 4. **(A)** Interaction between New York Heart Association (NYHA) functional class and renal function on brain natriuretic peptide (BNP) secretion (transcardiac increase of BNP). **(B)** Interaction between NYHA functional class and renal function on plasma BNP. Median values and patients' numbers are shown. Other abbreviations as in Figure 3.

McCullough et al. (4) reported for the first time that the optimal cutoff for BNP to diagnose CHF should be increased for patients with an eGFR <60 ml/min/1.73 m^2. Recently, Forfia et al. (5) reported that plasma BNP levels were approximately four-fold greater in patients with an eGFR <60 ml/min compared with that in patients with an eGFR >60 ml/min, despite similar hemodynamic overload. The present study supports their observations by the direct sampling of BNP from the coronary sinus and the aortic root at cardiac catheterization in 366 CHF patients.

There are several limitations to this study. The data on echocardiography were not measured, and there were few patients with an eGFR <30 ml/min, the standard division for chronic kidney disease (CKD); we included patients with an eGFR <40 ml/min. Therefore, further studies are needed to confirm our findings.

We are in the midst of a chronic epidemic of CHF and CKD worldwide. Although many previous studies supported the usefulness of BNP in the diagnosis and management of CHF patients, several limitations have been postulated. Because of the normal decrease in GFR with increasing age, the diagnostic cutoff for BNP depends on age. The present study indicates that renal function had a more direct effect on circulating BNP than previously recognized in CHF patients with CKD. In conclusion, decreased clearance from the kidney contributes to the elevated BNP in CHF patients with CKD, especially in patients with an eGFR <60 ml/min. The plasma BNP may be a potential cardiorenal marker in CHF patients with CKD.

Reprint requests and correspondence: Dr. Takayoshi Tsutamoto, Cardiovascular and Respiratory Medicine, Shiga University of Medical Science Tsukinowa, Seta, Otsu 520-2192, Japan. E-mail: tutamoto@belle.shiga-med.ac.jp.

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